Brain network reorganisation in an adolescent after bilateral perinatal strokes

Large bilateral strokes in adults are often fatal and typically lead to severe functional impairment with little potential for recovery.[1] By contrast, perinatal strokes are associated with variable functional outcomes, with as many as 25% of survivors having healthy motor and cognitive function.[2] Focal cortical injuries sustained in early childhood can be compensated for more quickly and more completely than those sustained later in life.[3] However, the mechanisms underlying cortical plasticity are only beginning to be understood.[4] We have done an exhaustive investigation of one of our patients (PS1; an adolescent male), who sustained large, bilateral perinatal strokes in 1999, but nevertheless had typical neurodevelopment and his injuries went unnoticed until he was 13 years old. The case of this patient underscores the challenge of an accurate prognosis in children after early-life cortical injury.

PS1 was referred to our neurology clinic (St Louis Children's Hospital, MO, USA) in November 2012, because of noted clumsiness of his right hand (video) when he played baseball; he was a left-handed pitcher on a youth baseball team.

PS1's medical history suggested that perinatal strokes occurred 3 weeks postnatally in the setting of dehydration and anaemia after persistent feeding intolerance, vomiting, and diarrhoea, but were not identified at the time (appendix p 2). His subsequent neurodevelopmental trajectory was notable only for a temporary gait asymmetry at 12 months and a persistent, strong left-hand preference. PS1 received speech therapy and reading assistance in early childhood, but attended regular schools throughout adolescence.

Structural MRI revealed extensive bilateral cystic cortical lesions (figure; appendix p 2). This MRI showed that he had lost an estimated 259 cm^3, or approximately 20%, of his total supratentorial brain volume because of his perinatal injury.

The large disparity between the extent of his brain injury and his functional status justified further investigation. PS1 scored within 2 SD of the mean of age-matched (15 years) standardised scores on intelligence quotient and cognitive function. Motor testing revealed a slight deficit of the right upper limb in strength,

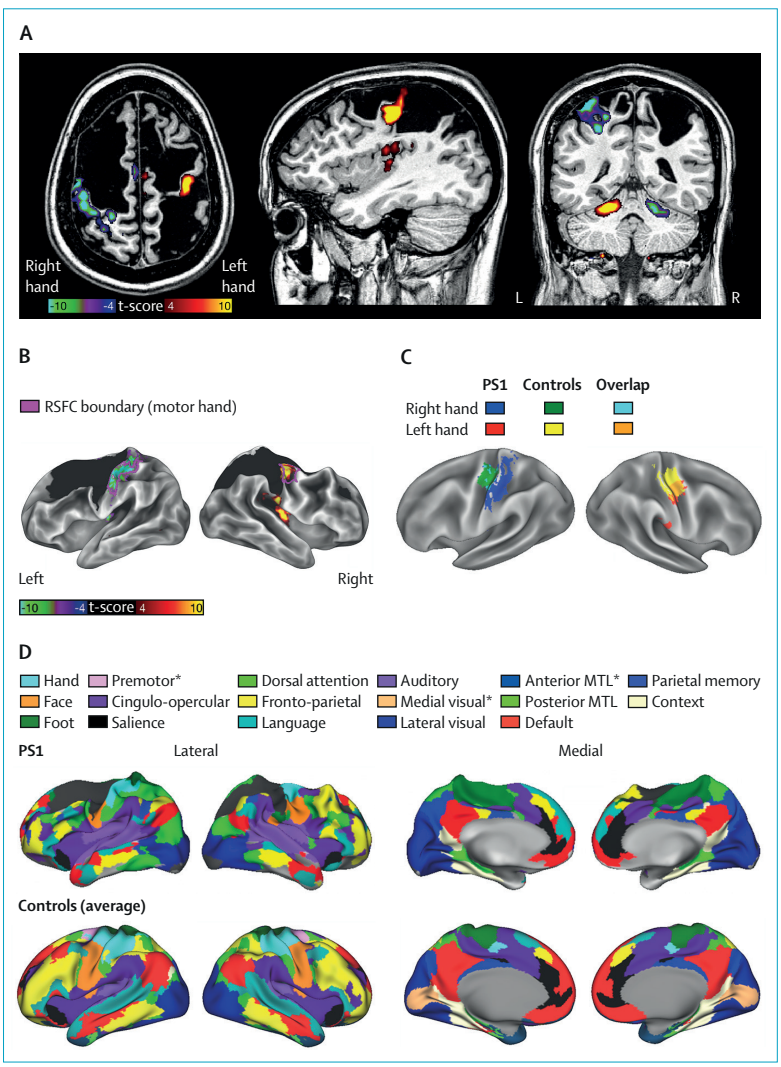

***Figure*: Functional brain network remapping in PS1 shown by task fMRI and RSFC**
(A) fMRI responses to unilateral hand motion (left *vs* right) overlaid on PS1's native space structural MRI that was T1-weighted. Left hand motor fMRI responses (shown in red and yellow) are preserved in intact regions of the motor system, including the spared right hemisphere central sulcus. Right hand motor fMRI responses (green and blue) are displaced to the left hemisphere postcentral gyrus. (B) Hand motor fMRI responses in PS1 overlap with the somatomotor network derived from PS1's RSFC data (magenta outline corresponds with the border of the somatomotor network). The t-score follows the same threshold as in (A). (C) Hand motor fMRI responses in PS1 compared with average location in healthy controls, with a threshold Z-score of 4. Data are projected on an average cortical surface. Left hand activity in PS1 falls nearly entirely within average fMRI response for control of the left hand (orange). Right hand activity in PS1 is completely displaced relative to the average fMRI response for control of the right hand (dark blue). (D) Functional network organisation of PS1 compared with the average of healthy controls. Note the grossly similar topological organisation of the networks (ie, similar spatial adjacency of functional networks). fMRI=functional MRI. MTL=medial temporal lobe. RSFC=resting state functional connectivity. *Networks that were identified in controls but not in PS1.

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See Online for appendix

speed, and dexterity relative to the left upper limb (appendix p 7).

Functional MRI (fMRI) has enabled the study of in vivo brain activity in response to tasks. fMRI can also measure patterns of correlated low frequency (<0·01 Hz) activity in resting, awake individuals (resting state functional connectivity [RSFC]).[5] RSFC reveals the brain's functional organisation at the systems level, including, for example, sensory, attention, executive control, language, and memory systems.[6,7] To investigate the remapping of brain function in PS1, we used a newly developed approach to individual-specific precision functional mapping (PFM).[8,9]

PS1 underwent extensive multi-session MRI scans at the East Imaging Building (St Louis, MO, USA) over two summers, beginning when he was aged 15 years (including 285 min of RSFC data and 137 min of task fMRI; appendix pp 3–7). Task fMRI and RSFC data were compared with data from healthy young adults (24–34 years, n=10, 5 female individuals, all right-handed) obtained with the use of the Midnight Scan Club protocol.[9] PS1 also underwent an extensive battery of motor and neurobehavioural assessments at the East Imaging Building, including the National Institutes of Health Toolbox (appendix p 3).

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Hand motor tasks showed intact fMRI responses in spared tissue. In the left hemisphere, where the primary motor cortex was nearly completely infarcted, fMRI response showed posterior remapping of function compared with healthy controls (figure A–C; appendix pp 8, 9). PS1's task-based fMRI responses closely aligned with his individual-specific functional network boundaries (figure B). Diffusion tensor imaging showed intact corticospinal tracts arising from both typical (left hand) and displaced (right hand) regions of motor task response (appendix p 10). Finally, RSFC showed a preserved overall organisation of the functional network in intact brain tissue (figure D), with near typical proportions of cortical surface dedicated to each functional network (appendix p 11). A detailed examination of brain network motifs (ie, the characteristic spatial arrangement of adjacent functional networks) suggested that remapping had occurred primarily in the frontal and parietal association areas (appendix p 12).

Functional network organisation in association areas is incompletely developed at term[10] and shows the greatest interindividual variability in adults.[8] Individual-specific variants in network organisation have been well documented in healthy individuals.[9] However, the number, extent, and pattern of deviations suggest that individual variability alone does not explain our findings in PS1.

Had PS1's infarcts been detected in infancy, his family would probably have been told to expect severe functional impairments. Much to the contrary, PS1 (now aged 22 years) has completed a degree from a technical college and is working in the automotive industry. Future studies that detail the potential for functional remapping relative to tissue loss are needed to provide more accurate prognoses and to understand the factors associated with favourable outcomes, such as those of our remarkable patient.

TOL and AZS are named on US patent 10 258 289 and TOL is named on US Patent Application 16/141 605. NUFD is named on US Patent Application 16/491,413 and is the cofounder of NOUS Imaging. All other authors declare no competing interests.

*Timothy O Laumann, Mario Ortega, Catherine R Hoyt, Nicole A Seider, the Brain Network Plasticity Group,† Abraham Z Snyder, Nico UF Dosenbach
laumannt@wustl.edu

†Members and affiliations in the appendix

Department of Neurology (TOL, MO, CRH, NAS, AZS, NUFD), Department of Radiology (AZS, NUFD), Department of Psychiatry (TOL), Department of Biomedical Engineering (NUFD), Department of Pediatrics (NUFD), and Program in Occupational Therapy (CRH, NUFD), Washington University, St Louis, MO 63110, USA

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